Applicants respectfully traverse these grounds of rejection since the amended claims are believed to properly define the invention. The Examiner's suggestion with respect to claim 1 has been adopted as well as the suggestion with respect to claim 2. Claims 3 to 7 now recite the diseases being treated. With respect to claims 4, 6, 7, 12 and 14, these are bone diseases and therefore, are properly dependent upon claim 3 and the same is true with respect to claims 5, 7, 13 and 15, these are directed to cartilage diseases. The application supports this limitation in line 22 of page 3. The terms "radicular" and "aleveolar defects" relate to dental defects. The Examiner's suggestion with respect to claims 9 and 10 have been adopted. Claims 11 to 15 are now proper method claims and are no longer indefinite and the Examiner's suggestion has been adopted. Therefore, withdrawal of these grounds of rejection is requested.

Claims 1, 2, 8 and 9 were rejected under 35 USC 102 as being anticipated by the Hotten et al reference since the Examiner is of the opinion that the expression "having" is open ended and does not exclude additional unrecited elements. These claims have been amended to use the term "consisting of" rather than "having" which is no longer open ended. Therefore, withdrawal of this ground of rejection is requested.

Claims 1, 2 and 10 were rejected under 35 USC 103 as being obvious over the Hotten et al reference taken in view of the

Cerletti et al reference and claims 1 to 7 and 11 to 15 were rejected under 35 USC 103 as being obvious over the Hotten et al reference taken in view of the Neidhardt et al reference. The Examiner deems that the results of Applicants' process for making a protein consisting of the amino acid sequence of SEQ ID No: 1 are unexpected and claims limited to such a process are deemed to be allowable.

Applicants respectfully traverse these grounds of rejection since the Hotten et al reference, whether taken alone or with the secondary references cited by the Examiner, would not teach Applicants' novel protein which has a sequence of 119 amino acids beginning with the proline residue as indicated in SEQ ID No: 1 which is novel with respect to the Hotten et al reference. The latter describes a GDF-5 protein with a much longer sequence of 501 amino acids as can be seen from Figs. 1 and 2. Hotten et al only suggests a mature protein of 120 amino acids commencing with a alanine residue. Therefore, the same does not render obvious Applicants' invention whether taken alone or in view of the secondary references.

With respect to the Examiner's statement that Hotten et al describes a dimer of GDF-5 and a plasmid containing "6 histidine tagged fragment of GDF-5 with a methionine at the M-terminus but he

as describing a process for the production of TGFB-like dimeric proteins biologically active obtained starting from the culture of E.coli and "inclusion bodies". The Examiner believes that this would be obvious to one skilled in the art for the preparation of a plasmid containing a nucleotide sequence coding for the sequence of the amino acids SEQ ID No: 1 with N-terminus methionine supplementary so that one skilled in the art would combine the two teachings to obtain a homodimer in the native form of GDF-5 with a reasonable degree of success.

With respect to the teaching of Hotten et al, it does not describe a plasmid containing 6-histidine tagged fragment of GDF-5 with a methionine at the N-terminus but only mentions the expression of "6-histidine tagged fragment of the mature GdF-5 (His-Gdf-5) in E.coli without any operating details on page 647. It is true that Hotten et al teaches that the active mature proteins of the TGF-ß family are produced by cleavage of a dimeric precursor protein and suggests a native dimer protein GdF-5 and a mature GdF-5 protein with 120 amino acids with the sequence as shown in Figure 1. It is true that Cerletti et al teaches a process for the production of dimeric TGF-ß-like proteins with a refolding of a denatured monomeric protein as set forth in claim 1. This would not teach a protein with 119 amino acids of the SEQ ID No: 1 of Applicants' invention or the corresponding homodimeric protein of claim 2. It is in no way suggested nor rendered obvious the teachings of the references. Hotten et al only suggests one

sequence of a mature GdF-5 sequence corresponding to the sequence of the claimed protein with a supplementary alanine residue in the N-terminal position. Any method of production of the TgF-5 mature protein in E.coli is not described or suggested. In E.coli, Hotten et al describes only the expression of a derivative (His-GdF-5) with the expected immunological properties and the use thereof to produce chicken antibodies. Therefore, this combination fails.

The same is true with respect to the combination of Hotten et al and the Neidhardt references. The Examiner indicates that the Neidhardt reference describes a MP-52 protein with a sequence of amino acids of SEQ ID No: 1 and describes the mature portion of MP-52 with a large portion of the sequence of propeptide (MP-52 is GdF-5 of Hotten et al). Neidhardt describes only a pharmaceutical composition containing MP-52 and its administration and does not describe any composition of a homodimer of MP-52. Neidhardt describes for MP-52 a sequence of 401 amino acids on page 19 of the reference as well as a sequence of 100 amino acids on page 20. Neidhardt indicates that the proteins of the BMP group have a C-terminal group of about 110 amino acids as a precursor which is cleaved and represents a mature protein on page 1. Neidhardt does not describe in any precise fashion the mature sequence of MP-52 nor suggests any sequence of 122 amino acids beginning with alanine described by Hotten et al for the protein GDF-5. Therefore, the combination of the prior art does not render obvious Applicants' invention and withdrawal of the same is requested.

In view of the amendments to the Abstract and the claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:ds
Enclosures